TENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
SCHMITZ, Yvon
Gevers Patents
Holidaystraat 5
B-1831 Diegem
BELGIQUE

23 NOV. 1998

Date of mailing (day/month/year): 12 November 1998 (12.11.98)	
Applicant's or agent's file reference: DPPC 402.012	IMPORTANT NOTICE
International application No.: PCT/BE98/00064	International filing date (day/month/year): 07 May 1998 (07.05.98)
Priority date (day/month/year): 07 May 1997 (07.05.97)	
Applicant: PHARLYSE, SOCIETE ANONYME et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,IL,JP,KP,KR,NO,PL,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,GW,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   12 November 1998 (12.11.98) under No. WO 98/50015

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer: J. Zahra

Telephone No. (41-22) 338.83.38

2333093

REJECTED

PATENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

To:

SCHMITZ, Yvon
Gevers Patents
Holidaystraat 5
B-1831 Diegem
BELGIQUE

NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENTS

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year)
04 June 1998 (04.06.98)

Applicant's or agent's file reference
DPPC 402.012

IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/BE98/00064	07 May 1998 (07.05.98)	07 May 1997 (07.05.97)

Applicant
PHARLYSE, SOCIÉTÉ ANONYME et al

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
97870065.6	07 May 1997 (07.05.97)	EP	29 May 1998 (29.05.98)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Marie-José Devillard
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
DPPC 402.012		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BE 98/ 00064	07/05/1998	07/05/1997
Applicant		
PHARLYSE, SOCI T ANONYME et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

XP 002044134

P.D. 1992
p. = 1

/1 - (C) FILE HCA
AN - 117:239737 HCA
TI - Consolidation and compaction of powder mixtures: III. Binary mixtures of different particle size fractions of different types of crystalline lactose
IN - Riepma, K. A.; Zuurman, K.; Bolhuis, G. K.; De Boer, A. H.; Lerk, C. F.
CS - Dep. Pharm. Technol. Biopharm., Univ. Groningen, Groningen, 9713 AV, Neth.
SO - Int. J. Pharm. (1992), 85(1-3), 121-8
CODEN: IJPHDE; ISSN: 0378-5173
DT - Journal
LA - English
AB - Tablets were compacted from a coarse fraction (250-315 .mu.m), a fine fraction (32-45 .mu.m) and from binary blends of a coarse and a fine fraction of different types of cryst. lactose. The results showed differences in consolidation and compaction between the granular lactose types, i.e., roller-dried .beta.-lactose and anhyd. .alpha.-lactose, and the non-granular lactose types, namely, cryst. .beta.-lactose and .alpha.-lactose monohydrate. Equal particle size fractions of the granular types of lactose exhibited greater specific powder surface areas, less fragmentation on compression, and higher binding capacities than the non-granular types. Slight increases in consolidation were demonstrated on compression of binary blends of the coarse and fine fraction of the different types of lactose. Differences in morphol. between the lactose types were shown by increasing true densities of the granular types when examd. on tablets compacted with increasing compression force. No change in true densities on compaction were demonstrated by the non-granular types.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 98/00064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 11179 A (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 8 August 1991 cited in the application see claims 1-21 ---	1-13
A	WO 95 24889 A (GLAXO GROUP LTD) 21 September 1995 see claims 1-17 see page 4, line 26 - page 5, line 12 ---	1-13
A	US 5 551 489 A (EVA A. C. TROFAST ET AL) 3 September 1996 see the whole document ---	1-13
A	US 3 802 914 A (R. L.NEZBED) 9 April 1974 see the whole document --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 1998	25/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 98/00064

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AN: 117:239737, K. A. RIEPMA ET AL: "Consolidation and compaction of powder mixtures: III. Binary mixtures of different particle size fractions of different types of crystalline lactose" XP002044134 & Int. J. Pharm. (1992), 85(1-3), 121-8 see abstract -----	1-13

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BE 98/00064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9111179 A	08-08-1991	AU 635616 B	25-03-1993
		AU 7155991 A	21-08-1991
		CA 2049302 A	25-07-1991
		DE 69100792 D	27-01-1994
		DE 69100792 T	14-04-1994
		EP 0464171 A	08-01-1992
		GB 2240337 A,B	31-07-1991
		JP 4504427 T	06-08-1992
		PT 96567 A	15-10-1991
		US 5254330 A	19-10-1993
		US 5376386 A	27-12-1994
WO 9524889 A	21-09-1995	AU 2068995 A	03-10-1995
		EP 0750492 A	02-01-1997
		ZA 9502049 A	21-12-1995
US 5551489 A	03-09-1996	AU 7826194 A	01-05-1995
		CZ 9600942 A	12-06-1996
		EP 0721331 A	17-07-1996
		FI 961430 A	29-03-1996
		HU 74519 A	28-01-1997
		NO 961290 A	29-03-1996
		PL 313765 A	22-07-1996
		WO 9509615 A	13-04-1995
		ZA 9407533 A	03-04-1995
		AU 679789 B	10-07-1997
		BR 9407686 A	04-02-1997
		JP 9504224 T	28-04-1997
		SK 39196 A	04-06-1997
		CN 1132476 A	02-10-1996
US 3802914 A	09-04-1974	CA 980768 A	30-12-1975

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00, 47/26

A1

(11) International Publication Number: WO 98/50015

(43) International Publication Date: 12 November 1998 (12.11.98)

(21) International Application Number: PCT/BE98/00064

(22) International Filing Date: 7 May 1998 (07.05.98)

(30) Priority Data:
97870065.6 7 May 1997 (07.05.97) EP
(34) Countries for which the regional or international application was filed: BE et al.

(71) Applicant *(for all designated States except US)*: PHARLYSE, SOCIETE ANONYME [LU/LU]; 2, boulevard Royal, L–Luxembourg (LU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: VANDERBIST, Francis [BE/BE]; Avenue des Jardinets 18, B–1170 Brussels (BE). MAES, Paul [BE/BE]; Rue Robert Ledecq, B–1440 Wauthier Braine (BE). BAUDIER, Philippe [BE/BE]; Avenue Blucher 10, B–1410 Waterloo (BE).

(74) Agents: SCHMITZ, Yvon et al.; Gevers Patents, Holidaystraat 5, B–1831 Diegem (BE).

(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: DRY POWDER INHALER EXCIPIENT, PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

(57) Abstract

A pharmaceutical excipient useful in the formulation of dry powder inhaler compositions comprising a particulate roller–dried anhydrous β–lactose, said β–lactose particles having a size between 50 and 250 micrometers and a rugosity between 1.9 and 2.4, and the so formulated pharmaceutical compositions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Replaced by art. 19 amendment

CLAIMS

1. A pharmaceutical excipient useful in the formulation of dry powder inhaler compositions, characterized in that it comprises a particulate roller-dried anhydrous β-lactose.

2. An excipient according to claim 1, characterized in that the roller-dried β-lactose particles have a size between 50 and 250 micrometers.

3. An excipient according to claim 2, characterized in that said particles have a size comprised between 100 and 160 micrometers.

4. An excipient according to any of claims 1 to 3, characterized in that said particulate roller-dried anhydrous β-lactose has a rugosity comprised between 1.9 and 2.4.

5. A dry powder inhaler pharmaceutical composition, characterized in that it comprises a mixture of an active ingredient and an excipient as claimed in any one of claims 1 to 4.

6. A composition according to claim 5, characterized in that the active ingredient is a particulate solid with a particle diameter comprised between 0.5 and 6 micrometers.

7. A composition according to either of claims 5 and 6, characterized in that the weight ratio of the active ingredient in relation to the excipient is of from 0.1/100 to 50/100.

8. A composition according to any of claims 5 to 7, characterized in that the active ingredient is selected from the group comprising mucolytics, steroids, sympathomimetics, proteins, peptides and inhibitors of mediator's release.

9. A composition according to claim 8, characterized in that the active ingredient is a mucolytic agent such as L-lysine N-acetylcysteinate.

10. A composition according to claim 9, characterized in that it comprises a mixture of particulate L-lysine N-acetylcysteinate and

roller-dried anhydrous β-lactose constituted by particles of 100 to 160 micrometers in size and of 1.9 to 2.4 in rugosity, the weight ratio of L-lysine N-acetylcysteinate in relation to the roller-dried anhydrous β-lactose being of from 1/2 to 1/6.

11. A composition according to claim 9, characterized in that the weight ratio of L-lysine N-acéthylcysteinate in relation to the roller-dried anhydrous β-lactose is comprised between 1/2 and 1/4.

12. A composition according to claim 11, characterized in that said weight ratio is of the order of 1/4.

13. A process for the preparation of an excipient as claimed in any one of claims 1 to 4, characterized in that anhydrous β-lactose in a powder form is dissolved in demineralised water, fed between two counterrotating drums, which are steam heated and then screeped from the surface of the drums.